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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,077	07/09/2004	Roland Kellner	MERCK-2907	3266

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EXAMINER	
MARTIN, PAUL C	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/501,077	KELLNER ET AL.	
	Examiner	Art Unit	
	Paul C. Martin	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5 and 8-10 are pending in this application and were examined on their merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All objections and rejections not repeated in the instant Action have been withdrawn due to Applicant's response to the previous Action.

Applicant's arguments with respect to claims 1-5 and 8-10 have been considered but are moot in view of the new ground(s) of rejection.

New Rejections (not necessitated by Applicant's amendment)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the detection of the phosphoamidase PHP1 by detecting the hydrolysis of the substrates FDP, DDAO, DiFMUP, ELF-39 and ELF-97 by PHP1, does not reasonably provide enablement for the detection of all phosphoamidases and/or the hydrolysis of a phosphor-ester bond of at least one of the substrates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. It is known in the art that certain phosphoamidases are able to hydrolyze nitrogen-phosphorus (N-P) bonds as well as oxygen-phosphorus (O-P), other phosphoamidases only hydrolyze (N-P bonds) and certain phosphoamidases only hydrolyze only phosphorylated arginine (Hiraishi *et al.* (1999) Column 1, Lines 1-24 & Column 2, Lines 1-6), therefore the instant invention will only be operable when O-phosphorylated substrates are exposed to phosphoamidase with the ability to hydrolyze both types of phosphorylations. At issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), *Amgen v. Chugai Pharmaceuticals Co. Ltd.*, 13 USPQ2d, 1737 (1990), and *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

In re Wands stated that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. As stated above the state of the prior art is such that phosphoamidases which are limited in the types of bonds that they will hydrolyze as well as those which can hydrolyze multiple bonds are known in the art. The instant specification provides working examples and guidance for the utilization of the invention for one specific phosphoamidase, with no explanation as to the operability of any other species of phosphoamidase enzyme. The skill level in the art is deemed to be high, however even one skilled in the art would be forced to perform undue experimentation in determining whether or not the phosphoamidase to be utilized would in fact hydrolyze the O-P bonds. Further, it is known in the chemical arts that P-O bonds can be hydrolyzed though alternate means, such as exposure to strong acids and that the mere hydrolyzing of the substrates as stated in Claim 1 through some unspecified means would not enable one of ordinary skill in the art to determine the presence or activity of a phosphoamidase. In light of these explanations, it is determined that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

Claims 1-5 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hiraishi *et al.* (1999) in view of Mountfort *et al.* (1999) and IUBMB Database [EC 3.9.1.1] (1961).

Hiraishi *et al.* teaches a phosphoamidase [EC 3.9.1.1] which can hydrolyze (N-P) bonds as well as (O-P) bonds in substrates and suggests that phosphoamidases may be identical to phosphoprotein phosphatase capable of hydrolyzing phosphohistidine (Pg. 368, Column 1, Lines 1-21).

Hiraishi *et al.* does not teach a method for the detection, characterization and quantitative and/or qualitative determination of the activity of a phosphoamidase, protein histidine phosphoamidase (PHP1) or a method for the identification of an inhibitor or activator of a phosphoamidase by establishing a sample comprising a phosphoamidase and a test substance, administering a substrate selected from the group consisting of FDP, DDAO, DiFMUP, ELF®39 phosphate or ELF®97 phosphate to the sample, detecting the signal produced by the hydrolysis of the phosphor-ester bond (P-O) of the substrate, and identifying the test substance as an activator or inhibitor of the phosphoamidase by comparing the signal produced in the sample comprising the test substance with the signal produced in a control sample.

The IUBMB (International Union of Biochemistry and Molecular Biology) Enzyme Nomenclature Database also suggests that phosphoamidase may be identical to phosphoprotein phosphatase and glucose-6-phophatase (Comments, Lines 5-6).

Mountfort *et al.* teaches the use of the substrate FDP (fluorescein diphosphate) for the detection and quantitative determination of the activity of a protein histidine phosphatase 2a (Pg. 914, Table 1).

Mountfort *et al.* teaches a method for the identification of an inhibitor of a phosphatase comprising:

a) establishing a sample comprising a phosphoamidase and a test substance,

b) administering the substrate FDP to the sample,

c) detecting the signal produced by the substrate,

d) Identifying the test substance as an inhibitor of the phosphatase by comparing the signal produced in the sample containing the test substance with the signal produced in a control sample with no test substance (Pg. 911, Lines 20-29 and Pg. 912, Lines 1-3 and Pg.914, Table 1 and Pg. 915, Fig. 2).

It would have been obvious to one of ordinary skill in the art to adapt the teachings of Hiraishi *et al.*, which states the known ability of phosphoamidases to catalyze both (N-P) and (N-O) bonds to known methods of enzyme assay such as that taught by Mountfort *et al.* for the detection and quantitative determination of the activity of a protein histidine phosphatase using the substrate FDP to the detection of protein histidine phosphoamidase because this would allow the determination of phosphoamidase activity through its catalytic action on fluorescent substrates. One of ordinary skill in the art would have been motivated to make these changes in order to more quickly measure and determine the presence and action of a protein histidine phosphatase. One of ordinary skill in the art would have recognized that as the teachings of Hiraishi *et al.* and the IUBMB teach and suggest that phosphoamidases [EC 3.9.1.1] are able to catalytically hydrolyze O-P bonds as well phosphohistidine that the specific use of the claimed substrates and PHP1 would have been an obvious variant of the phosphoamidases described by Hiraishi *et al.* because PHP1 would fall into Enzyme classification 3.9.1.1 as a phosphoamidase capable of catalyzing substrates containing phospho-ester bonds. There would have been a reasonable expectation of success in making these adaptations because Hiraishi *et al.* teaches the ability of phosphoamidases to catalyze both (N-P) and (N-O) bonds and the substrates used in the method of Mountfort *et al.* and the instantly claimed invention would be catalyzed by the phosphoamidases in class [EC 3.9.1.1].

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one with ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence or evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1655

07/12/06

PATRICIA LEITH
PRIMARY EXAMINER